



RETROSPECTIVE: ALZHEIMER'S DISEASE RESEARCH

AN OVERVIEW OF 1998–2015 GRANTMAKING
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“Though those with Alzheimer’s might forget us, we as a society must remember them.”

– Scott Kirschenbaum, Filmmaker



Clockwise from Top Left: The new Neurobehavioral Lab at the Gladstone Institutes; Dr. Stephen Bonasera of UCSF; the weMark Project website from Boston University; The 2012 Alzheimer's Association Northern California Research Symposium.

SUMMARY OF SUPPORT

The Foundation's Alzheimer's disease grantmaking consisted of support for the work of 15 scientists, seven multidisciplinary research centers, and a regional scientific symposium beginning in 1998. Final payments on grants awarded were made in 2015. Overall, the Foundation invested \$19.2 million, making 47 grants to seven organizations across five states (California, Maryland, Massachusetts, Illinois, and Alabama).



BACKGROUND

Thankfully, today many diseases around the world are in decline. Advances in public health, sanitation, and medical research have reduced the toll of numerous infectious and chronic diseases where we once had no response. The same cannot be said of Alzheimer's. Given that its primary risk factor is age, its incidence is on the rise in the United States, as well as much of the developed world. Physicians, policy makers, and economists increasingly warn that the human and financial costs of this epidemic will be sizable as our population ages, and are shepherding more resources toward understanding and treating it. However, the National Institute of Aging's budget currently is just 3% of all NIH appropriations,¹ and scientific progress has been slow with currently approved drugs promising only minimal benefits.

Beginning in 1998, in response to interest on the part of the S. D. Bechtel, Jr. Foundation Board of Directors, Foundation staff investigated options for supporting Alzheimer's disease research. The decision was made to fund basic research into the causes of the disease. Two experts in the field, Dr. Knight Steel and Dr. Seth Landefeld, were consulted and both suggested making grants to support the work of talented junior scientists. With the advice of Dr. Steel and Dr. Landefeld, the Foundation supported seven institutions for a total of \$19.2 million that supported the work of 15 promising scientists. The wisdom of the focus on young scientists was reinforced by a 2008 report from the American Academy of Arts and Sciences that stated:

First and foremost we must support early-career faculty and encourage high-risk, high-reward, and potentially transformative research.

¹ National Institutes of Health. *History of Congressional Appropriations, Fiscal Years 2000–2013*. Retrieved from <http://officeofbudget.od.nih.gov/pdfs/FY15/Approp%20%20History%20by%20IC%20through%20FY%202013.pdf>.

The following report covers the research and careers of these scientists by institution, and details how each grant accelerated their work and careers. From supporting new investigator fellowships to funding a regional research symposium, the Foundation's grantmaking addressed the growing need for Alzheimer's research in a consistent, time-sensitive, and human capital-driven way. Each one of the scientists supported by the Foundation has gone on to a noteworthy career with many running their own labs. And, as a group they have significantly contributed to the medical community's understanding and treatment of this disease. The Foundation's grantmaking to the field of Alzheimer's research came at a time when funding for early-stage investigators was limited and difficult to come by. In the intervening years, new funding streams and interdisciplinary research centers have buoyed the Foundation's investment and the work of these scientists.

List of Researchers Supported by the Foundation, with Current Affiliations:

Stephen Bonasera, *University of Nebraska Medical Center*

Jose Miguel Borreguero, *Oak Ridge National Laboratory*

Michelle Carlson, *Johns Hopkins University*

Veronica Galvan, *University of Texas at San Antonio*

Li Gan, *Gladstone Institutes and UCSF*

Michael Keiser, *UCSF*

Sei Lee, *UCSF*

Amy Manning-Bog, *SRI International and UC Santa Cruz*

Jorge Palop, *Gladstone Institutes and UCSF*

Clare Peters-Libeu, *Buck Institute*

Edgar Pierluissi, *UCSF*

Rammohan Rao, *Buck Institute*

Erik Roberson, *University of Alabama at Birmingham*

Jan Stoehr, *UCSF*

Brigita Urbanc, *Drexel University*

Dale Bredesen, *Buck Institute* (Supervisor)

Lennart Mucke, *Gladstone Institutes and UCSF* (Supervisor)

JOHNS HOPKINS UNIVERSITY

5 GRANTS FROM
2004–08
TOTALING \$275,000



Dr. Michelle Carlson

Located in Baltimore, Maryland, the Johns Hopkins University is an internationally recognized institution of higher learning. Its medical campus and hospitals consistently rank among the top nationally for clinical care and research.

The Foundation's grants to Johns Hopkins supported the award-winning work of **Dr. Michelle Carlson**, who is a core faculty member at the Center on Aging and Health. Her work focuses on identifying physical markers for early dementia, and evaluating interventions for those at risk before the full-blown effects of the disease take hold.

What makes Dr. Carlson's work so compelling is that even among the few treatments of Alzheimer's disease that show promise, they do little to deal with the debilitating cognitive decline that accompanies the neurological damage. The first grant made to support her work was in 2004, and funded the testing of a novel computer-based tool to detect and track preclinical changes associated with the progression of Alzheimer's disease. When initially contacted about the possibility of a grant, Dr. Carlson wrote:

Your support of this novel line of work comes at a critical time as Dr. Fried and I have a window of opportunity to develop and integrate potentially more sensitive techniques in the assessment of a cognitive activity intervention.

This was followed by a second grant in 2005 to develop and maintain a database to store the data relevant to this project. In 2006, the Foundation expanded its impact on the Carlson Lab by funding the initial testing of a computerized instrument that assesses cognitive frailty and brain functioning. In 2007, a fourth grant was made to connect executive functioning with brain changes and physical well-being, and a final grant was made in 2008 to spur research on aging's effect on memory and functional decline. That final grant helped Dr. Carlson's team scale their recruiting efforts, and exceed their annual goals for participation in their research studies.

The funding culminated in a paper for the *Journal of Gerontology*, for which Dr. Carlson was the lead author². The paper demonstrated MRI evidence of short-term gains in executive functioning for adults at elevated risk for cognitive impairment based on a social service-based intervention, and highlighted the plasticity of the older adult brain.

² Carlson, M. C., Erickson, K. I., Kramer, A. F., Voss, M.W., Bolea, N., Mielke, M., et al. (2009). Evidence for neurocognitive plasticity in at-risk older adults: the experience corps program. *Journal of Gerontology*. Series A, Biological Sciences and Medical Sciences, 64, 1275–1282.

BOSTON UNIVERSITY, CENTER FOR POLYMER STUDIES

6 GRANTS FROM
2004–11
TOTALING \$735,000

The Center for Polymer Studies at Boston University (BU) is devoted to interdisciplinary research that ranges from biomedical sciences to network theory and economics. Among its priorities is the study of Alzheimer's disease through the lens of statistical mechanics. The Foundation supported a new post-doctoral fellowship to study the folding of small proteins implicated in Alzheimer's disease. That fellowship was awarded to **Dr. Jose Miguel Borreguero** in 2004.

Although this gift was initially conceptualized as a "one-time personal contribution," the fellowship continued for the next three years, providing \$160,000 in total. Following his time as a Bechtel Fellow, Dr. Borreguero was awarded a three-year postdoctoral fellowship at the Center for Excellence in Bioinformatics at SUNY Buffalo, and is now an investigator at the Oak Ridge National Laboratory in Tennessee, part of the federal Department of Energy.

In 2005 and 2006, a concurrent fellowship was provided to **Dr. Brigita Urbanc**, who used physics-based models to predict what sites in the brain might be more amenable to Alzheimer's treatments. One of the articles directly supported by this fellowship was published³ in the *Proceedings of the National Academy of Sciences*, a preeminent scientific journal. Michael Dettelbach, the director of BU's office of Corporate and Foundation Relations wrote to the Foundation:

This kind of consistent support for young investigators is precisely what is needed to create new generations of researchers who address pressing problems, like the mechanisms of neurodegeneration in Alzheimer's disease, by venturing across disciplinary boundaries.

Starting in 2008, the amount of giving for the BU fellowship more than doubled from \$60,000 to 150,000 per year until 2010. The increased funding allowed the Center to bring greater quantitative rigor to bear on Alzheimer's research, and stimulated work on automated techniques for characterizing the architecture of brain networks.

The final grant made to the Center allowed the work on automated brain architecture to be turned into an accessible online resource called "weMark." This project brought together several other institutions engaged with this type of research, including the University of Massachusetts, UCLA, and the University of Arizona. Dr. Urbanc is now an associate professor of physics at Drexel University, where she continues to study the physical basis of Alzheimer's disease.

³ Borreguero, J. M., Urbanc, B., Lazo, N. D., Buldyrev, S. V., Teplow, D. B., Stanley, H. E. (2005). Folding events in the 21–30 region of amyloid- β -protein (A β) studied in silico. *Proceedings of the National Academy of Sciences*, 102, 6015–6020.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

5 GRANTS FROM
2004–12
TOTALING \$1.7 M

Solely dedicated to graduate medical and health sciences, University of California, San Francisco (UCSF) represented an ideal partner for the Foundation. From 2004 to 2007, the Foundation made three grants to the department of geriatrics totaling \$160,000 in support of **Dr. Stephen Bonasera's** research. Dr. Bonasera created a compelling model of Alzheimer's disease in mice that investigated how brain changes correspond to specific types of behaviors. The scope of this work also grew to include the study of how the mammalian genome changes with age, as well as a mouse model of delirium, a condition that strikes many end-stage Alzheimer's patients. Annual reports from the lab indicate that the grants made this level of analytic complexity possible, and let the staff take risks they may not have otherwise taken. At the conclusion of these research projects, Dr. Bonasera transitioned to running his own lab at the University of Nebraska Medical Center, where he continues to probe how the brain ages. In his final letter to the Foundation, he wrote:

Ultimately, foundation support has proven instrumental for my newest transition into an independent laboratory . . . the generous support of the S. D. Bechtel, Jr. Foundation and the National Institutes of Health have given me the opportunity to move my career and research goals to the next level of sophistication and complexity.

In 2008, the Foundation supported another early-career scientist at UCSF with a three-year grant to support the work of **Dr. Edgar Pierluissi**, who studies risk factors for Alzheimer's disease. With a strong record of scholarship and leadership (serving as chief resident at UCSF), Dr. Pierluissi, as then described by his mentor, was "at a critical point in his academic career when he needs to consolidate his research skills and initiate work that can be transformative."

There are physical and cognitive signs and symptoms that can signal someone is at an increased risk of developing the disease later in life, and are crucial to prevention. Dr. Pierluissi's research specifically examined the role that hospitalizations can play in exposing individuals to later risk for Alzheimer's, in part because it is highly associated with so many other known risk factors. The grant also supported him in creating a core group of researchers engaged with this topic. This work and the resulting publications⁴ led Dr. Pierluissi to be promoted to associate professor at UCSF.

The third early investigator funded by the Foundation in the UCSF department of geriatrics was **Dr. Sei Lee**, whose work deals with Alzheimer's diagnosis testing technology. These tests have high false-positive rates, which can lead to unnecessary treatments for older adults.

⁴ Covinsky, K.E., Pierluissi, E., Johnston, C.B. (2011). Hospitalization- associated disability: "She was probably able to ambulate, but I'm not sure". *Journal of the American Medical Association*, 306, 1782–1793.

To avoid this, Dr. Lee's research focuses on the biological changes that lead to Alzheimer's disease, to model early attempts at diagnosis on biological processes that are more likely to lead to dementia. Dr. Lee is now an associate professor at UCSF, and has continued his work to improve the targeting of preventive interventions for Alzheimer's disease, to maximize benefits and minimize harm.

In 2012, the Foundation looked to UCSF's new Institute for Neurodegenerative Diseases (IND) as a source of innovation in Alzheimer's research. IND is at the forefront of diagnosing and developing therapies that can provide relief for those suffering from neurodegenerative diseases, with Alzheimer's disease being a significant focus of their work. Following a meeting with the IND Director and Nobel Laureate Stanley Prusiner, the Foundation made a two-year pledge totaling \$500,000 to support the work of two early stage investigators to conduct research on neurodegenerative diseases.

The scientists who were able to join the IND because of this funding were **Dr. Jan Stoehr** and **Dr. Michael Keiser**. Dr. Stoehr's research involves prions, an infectious agent made from misfolded protein that has been hypothesized to be involved in almost all neurodegenerative disorders including Alzheimer's. Dr. Keiser's work involves therapeutics, and creating predictions for individual drug responses. The work of both scientists was supported by grants in 2012 and 2013, and they remain at the IND as assistant professor and instructor, respectively.



Dr. Edgar Pierluisi visits with Mrs. Devera before she goes home from the ACE Unit at SFGH.

Dr. Edgar Pierluisi in the UCSF Aging Newsletter



Dr. Sei Lee

J. DAVID GLADSTONE INSTITUTES

10 GRANTS FROM
2004–11
TOTALING \$8.9 M

The Gladstone Institutes, based in San Francisco, are independent, nonprofit biomedical research organizations whose focus is to better understand, prevent, treat, and cure cardiovascular, viral, and neurological conditions. The Institutes are financially independent but closely affiliated with UCSF, and many of their scientists hold joint positions on the UCSF faculty.

The Foundation's giving to the Gladstone Institutes began with the work of **Dr. Erik Roberson**, who from 2004 to 2007 was provided funds to further his work studying tau proteins, a neurological hallmark of Alzheimer's disease. **Dr. Lennart Mucke**, the pioneering director of the Neurological Institute at Gladstone, wrote that the Foundation's support has been "indispensable to Erik's ability to pursue highly innovative and productive avenues of investigation involving Alzheimer's disease." He added that the Foundation's "philanthropic investment in our work at a critical point in Erik's 'post-postdoctoral' training has played a pivotal role in the career development of this outstanding young investigator." Following Dr. Roberson's promotion to a professorship at the University of Alabama in 2008, the Foundation transferred the remaining funding to his new lab, which is discussed further below.

In the years that followed, the Foundation's grantmaking to the Gladstone Institutes continued to support young researchers, and included a significant capital investment (\$6 million) for the development of the Center for Comprehensive Alzheimer's Disease Research. On the occasion of the founding of this center, Dr. R. Sanders Williams, president of the Gladstone Institutes, wrote to the Foundation:

We have determined aspirations for preventing, treating, and perhaps even curing Alzheimer's. With your commitment to help us create a Center for Comprehensive Alzheimer's Disease Research, we now have the cornerstone necessary to reach our ambitious goals.

This comprehensive approach to Alzheimer's disease bridges the divide between traditional academic medicine and private pharmaceutical companies. The Institute's interim report to the Foundation in 2012 stated that the funding for the center enabled them to exceed all of their Year One aims. They also leveraged the gift to generate additional funding. In 2014, Dr. Mucke wrote that they had successfully launched their first clinical trial that highlighted the overlap between Alzheimer's disease and epilepsy, identified new strategies to counteract age-related cognitive deficits, and secured additional funding ahead of schedule.

Grants were also provided to support the work of a promising young investigator, **Dr. Li Gan**, whose research focuses on the loss of neurons in Alzheimer's disease. It should be noted that the Foundation's grant to support Dr. Gan's work was critical given the sudden, unexpected withdrawal of NIH funding from her program in 2009. Other early stage investigator support made possible the research of **Dr. Jorge Palop**, focused on the cognitive decline associated with Alzheimer's disease. Dr. Palop's work, funded by the Foundation for four full years, has been widely acknowledged in the field, and his articles have appeared in the top medical and scientific journals, including *Nature*.⁵ Both Dr. Gan and Dr. Palop continue to study Alzheimer's disease at the Gladstone Institutes.



Dr. Li Gan



Dr. Jorge Palop

⁵ Palop J. J., Chin J., & Mucke L. (2006). A network dysfunction perspective on neurodegenerative diseases. *Nature*, 443, 768–773.

BUCK INSTITUTE FOR RESEARCH ON AGING

10 GRANTS FROM
2001–11
TOTALING \$3.42 M

The Buck Institute is an independent research facility focused solely on understanding the connection between aging and chronic disease. Alzheimer's disease is a priority for the Institute, and the Foundation's initial gift was a \$50,000 grant to purchase strategic hardware for its core gero-informatics facility in 2001. The following year, the Foundation supported a summer intern program for high school students. A grant report noted that this program had "become so successful that current demand far exceeds the available spaces," and the program received significant positive coverage in local media.

In 2006, the Foundation provided a grant of \$100,000 to the Buck Institute to support the work of **Dr. Veronica Galvan**, a young investigator whose work in mouse models of Alzheimer's highlighted specific genes that play a role in disease development. Dr. Galvan was the lead author of a paper covering the gene in question in the *Proceedings of the National Academy of Sciences*,⁶ one of the top scientific journals in the world. Since that time, Dr. Galvan has been appointed assistant professor at the University of Texas, San Antonio, where she directs her own lab and continues to study molecular pathways in Alzheimer's and potential treatments.

In 2008, the Foundation deepened its relationship with the Buck Institute with a three-year grant for \$450,000 to support the work of other young investigators. **Dr. Clare Peters-Libeu** was supported by this grant for work to investigate the precursor protein to beta amyloid, another hallmark of Alzheimer's disease. Buck scientists have theorized that beta amyloid and its precursor protein represent a molecular "switch" that mediates brain connection formation and loss. Dr. Peters-Libeu's work investigated that theory with cutting edge crystallography. She still works at the Buck Institute, and has been promoted to staff scientist.

The final two grants provided to the Buck Institute were made in 2011, and they were significant in their size and purpose. The first was a three-year grant to support the work of **Rammohan Rao, Ph.D.**, a young investigator studying how the misfolding of proteins can lead to cellular death. Dr. Dale Bredesen, the founding president of the Institute outlined Dr. Rao's exceptional work: "Dr. Rao has become one of the international leaders in this field . . . [and] has been the most productive scientist here in terms of publications." This work has helped him earn the position of associate professor at the Institute.

⁶ Galvan V. et al. (2006). Reversal of Alzheimer's-like pathology and behavior in human APP transgenic mice by mutation of Asp664. *Proceedings of the National Academy of Sciences*, 103, 7130–5.

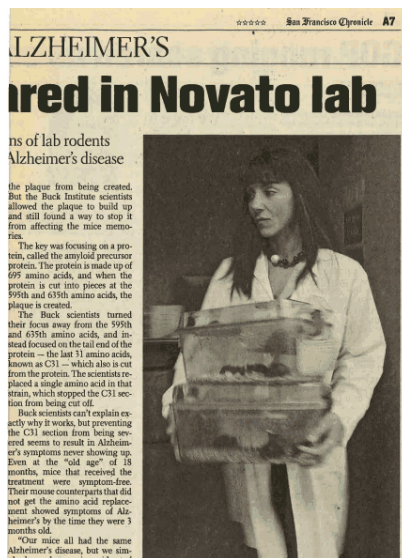
The second grant, a two-year grant for \$2 million, was provided for the development of a systems therapeutics approach to Alzheimer's disease. Given the molecular complexity of Alzheimer's disease, the hypothesis driving this approach is that Alzheimer's cannot be solved with a single drug, but rather a combination of therapeutics that target the physiological imbalances at play.

This grant was particularly meaningful in the context of novel therapeutics because there remains a gap in the way medical research is currently funded. The NIH will traditionally fund drug discovery, but not clinical trials, and pharmaceutical companies fund just the opposite. It is much harder to get funding for the entire pipeline of research and testing needed to tackle a stubborn disease. Dr. Bredesen discussed this topic directly in a report to the Foundation:

We are especially grateful to the S. D. Bechtel, Jr. Foundation because the novel studies we are undertaking with the Foundation support would not be supported by standard academic funding agencies.

As of 2011, a clinical trial of this combined therapeutics method has been initiated in Australia, with hopes for a second clinical trial in the US. This trial not only offers hope for a new treatment, but truly a new *class* of treatments, that could show whether a networked approach fares better than traditional monotherapies.

This approach did not proceed without setbacks, however. The scientific review board in Australia rejected the combined approach in 2013, making the research team break their clinical trial into two separate trials. That second application was approved. The work is now under way, and Dr. Bredesen's team has since published scientifically-acclaimed work linking two previously little understood risk factors for dementia.⁷



Dr. Veronica Galvan, featured in the
San Francisco Chronicle

⁷ Theendakara, V., Patent, A., Peters-Libeau, C.A., Philpot, B., Flores, S., Descamps, O., Poksay, K.S., Zhang, Q., Cailing, G., Hart, M., John, V., Rao, R.V., Bredesen, D.E. (2013). Neuroprotective Sirtuin ratio reversed by ApoE4. *Proceedings of the National Academy of Sciences*, 110(45), 18308-8.

ALZHEIMER'S ASSOCIATION

9 GRANTS FROM
2001–13
TOTALING \$871,500 M

The Alzheimer's Association is a leading health organization focused on care, support, and research. The Foundation's support for the Alzheimer's Association was significant and varied, providing funding for building renovations, as well as a 24-hour phone line for caregivers of individuals with dementia. The largest initiatives supported were the launching of a Northern California Alzheimer's Research Symposium and a New Investigator Award, both of which began in 2008. Giving to both programs continued annually through 2013, and together totaled close to \$800,000.

The Association emphasized that the Foundation's support was critical at that time because federal funding for research had not kept pace over the last decade. The National Institute of Aging's (part of NIH) funding rate dropped from 20% of grants to 10%, while the number of American's living with Alzheimer's disease is forecasted to increase 300% by 2030.

One of the first scientists supported by this award was **Dr. Amy Manning-Bog**. Dr. Manning-Bog studied the role of a specific gene that is associated with cognitive impairment, and Parkinson's disease. This portion of her career continues to influence her work on the intersecting pathways of degenerative diseases, as the manager of the Neurodegenerative Diseases Program at SRI International.

The research symposium provides a chance for the sizable Alzheimer's research community in Northern California to gather in an invitation-only, peer-to-peer environment, at no charge to the attendees. That is notable given that most scientific conferences require a considerable registration fee. A report from the Alzheimer's Association reads "This is the ONLY time each year that our entire local Alzheimer's disease research community comes together . . . Attendees describe this event as the most important professional meeting of their year."

In 2009, the Alzheimer's Association published a report on philanthropies' impact in the field, and dedicated two pages to an acknowledgement of the S. D. Bechtel, Jr. Foundation's support. Program Director Marcia Argyris was quoted in the article:

We think this process of bringing together so many talented people – from most senior to most junior – to determine best-in-field proposals is critical to keeping researchers engaged and excited, and we wanted to support this peer review process.

The Foundation's consistent support of this symposium helped it expand to a record high of 150 attendees in 2011 and to grow some of its programming. In 2012, the Foundation supported a new addition to the symposium, called the Student Awards for Excellence in Research. These cash prizes were awarded for scientific contributions from those studying Alzheimer's disease at the undergraduate, graduate, or post-graduate level, to encourage further interest in the field among the next generation of scientists.

It is also notable how the Foundation's giving to the Alzheimer's Association spurred other funders to join the cause. In a 2011 letter from Harold Rosenblume, the Association's director of the West Region, wrote that "We are thrilled to report that your Foundation's \$150,000 anonymous challenge match for our nationwide year end direct mail appeal resulted in over \$4 million from donors all over the country who responded to your challenge."



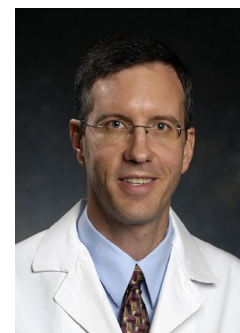
Dr. Amy Manning-Bog



The 2012 Alzheimer's Association Northern California Research Symposium

UNIVERSITY OF ALABAMA AT BIRMINGHAM

2 GRANTS FROM
2009–10
TOTALING \$130,000



Dr. Erik Roberson

Dr. Erik Roberson was, until 2008, a researcher at the Gladstone Institutes and supported by funding from the Foundation. At that time, he was offered a tenure-track position at the University of Alabama at Birmingham (UAB), which gave him the opportunity for stability and growth of his lab. He is now an associate professor in the department of neurology at UAB, and his research continues to focus on the neurobiology of Alzheimer's disease and generalized dementia.

Following his move to UAB, the Foundation made two grants to continue its support of Dr. Roberson's research. The first grant was a matching grant for \$30,000 in 2009, to combine with funding from the University's Alzheimer's Disease Research Center, to look for subclinical seizures in patients with Alzheimer's, as has been documented in animal models of the disease.

In 2010, a final grant was made for \$100,000, and went specifically to Dr. Roberson's attempts to delineate the role of tau in neurodegeneration. On this occasion, Dr. Roberson wrote:

For the past several years, funding from the Stephen Bechtel Fund has provided critical support for my laboratory's research on the role of tau in neurodegeneration. . . . We have made considerable progress in understanding how tau contributes to the cognitive and behavioral symptoms in Alzheimer's disease and related disorders and are working to translate these findings into better treatments.

Since that time, Dr. Roberson has continued his work at UAB, publishing his findings in high-quality medical journals such as *PLOS ONE*⁸, and further implicated tau in a variety of features of neurodegeneration.

⁸ Roberson, E.D., Pevsner, J. (2009). Visualization of shared genomic regions and meiotic recombination in high-density SNP data. *PLOS ONE*,4, e6711.

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